

Effects of psilocybin on time perception and temporal control of behaviour in humans

Journal of Psychopharmacology
 21(1) (2007) 50–64
 © 2007 British Association
 for Psychopharmacology
 ISSN 0269-8811
 SAGE Publications Ltd,
 London, Thousand Oaks,
 CA and New Delhi
 10.1177/0269881106065859

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Abstract

Hallucinogenic psilocybin is known to alter the subjective experience of time. However, there is no study that systematically investigated objective measures of time perception under psilocybin. Therefore, we studied dose-dependent effects of the serotonin (5-HT)_{2A/1A} receptor agonist psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) on temporal processing, employing tasks of temporal reproduction, sensorimotor synchronization and tapping tempo. To control for cognitive and subjective changes, we assessed spatial working memory and conscious experience. Twelve healthy human volunteers were tested under placebo, medium (115 µg/kg), and high (250 µg/kg) dose conditions, in a double-blind experimental design. Psilocybin was found to significantly impair subjects' ability to (1) reproduce interval durations longer than 2.5 sec, (2) to synchronize to inter-beat intervals longer than 2 sec and (3) caused subjects to be slower in their preferred tapping rate. These objective effects on timing performance were accompanied by working-memory deficits and subjective changes in conscious state,

namely increased reports of 'depersonalization' and 'derealization' phenomena including disturbances in subjective 'time sense.' Our study is the first to systematically assess the impact of psilocybin on timing performance on standardized measures of temporal processing. Results indicate that the serotonin system is selectively involved in duration processing of intervals longer than 2 to 3 seconds and in the voluntary control of the speed of movement. We speculate that psilocybin's selective disruption of longer intervals is likely to be a product of interactions with cognitive dimensions of temporal processing – presumably via 5-HT_{2A} receptor stimulation.

Keywords

psilocybin, 5-HT_{2A} receptor, temporal processing, sensorimotor synchronization, altered states of consciousness, working memory, human study

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Introduction

Events are perceived over time, and motor actions evolve over time. The brain, therefore, has to process temporal information adequately for the control of perception and action. Evidence to date suggests that different temporal-processing mechanisms are implemented in distinct circumscribed neural circuitries that can be affected by brain injury and pharmacological treatments (Harrington and Haaland, 1998; Rammssayer, 1999; Wittmann, 1999). Accuracy and precision of time estimation and the exact timing of motor behaviour are intimately linked to overall cognitive functioning. Basic timing processes (internal clocks) are an integral part of the whole cognitive system (Steinbüchel and Pöppel, 1993; Wearden, 2004). Patients with structural damage to the brain such as with right-hemispheric focal brain lesions following a stroke (Kagerer *et al.*, 2002) or with traumatic brain injury dominantly affecting frontal areas (Pouthas and Perbal, 2004), patients with dysfunctions related to the dopaminergic system of the brain such as in Parkinson's disease (Pastor *et al.*, 1992) or in schizophrenia (Elvevag *et al.*, 2003), but also healthy older adults (Block *et al.*, 1998) can show substantial impairments in temporal processing. Specifically, these populations show more variability and deviate more strongly from target durations during tasks involving time estimates and the timing of motor acts. These findings are discussed in relation to alterations on several information-processing stages related to time processing, specifically a clock, memory and decision stage (Wearden, 2004) as well to attentional mechanisms (Zakay and Block, 1996). Specifically, recent studies report that schizophrenic patients show deficits in discriminating temporal durations (Volz *et al.*, 2001; Davalos *et al.*, 2002; 2003; Elvevag *et al.*, 2003) as well as recognizing the temporal order of visual and acoustic stimuli (Braus, 2002; Tenckhoff *et al.*, 2002).

Recent research into the pharmacological mechanism of hallucinogens (LSD, psilocybin) and dissociative anesthetics (PCP, ketamine) suggests that a dysbalance between serotonin, glutamate and dopamine neurotransmitter systems may be critical to psychotic symptom formation (Vollenweider, 1998). Specifically, there is increasing evidence that the serotonin 5-HT_{1A/2A} receptor systems are involved in psychotic symptom formation as well as the cognitive and behavioural deficits of schizophrenia (Mita *et al.*, 1986; Arora and Meltzer, 1991; Ngan *et al.*, 2000; Bantick *et al.*, 2001; Roth and Hanizavareh, 2004). Receptor binding studies in rats have shown that psilocin (4-Hydroxy-N,N-dimethyltryptamine), the pharmacologically active metabolite of psilocybin (Hasler *et al.*, 1997), primarily binds to 5-HT_{2A} receptors ($K_i=6\text{ nM}$) and with a lower affinity also to the 5-HT_{1A} sites ($K_i=190\text{ nM}$) (McKenna *et al.*, 1990). Psilocybin induces a model psychosis which mimics certain aspects of acute and incipient stages of schizophrenia (Gouzoulis-Mayfrank *et al.*, 1998; Klosterkötter *et al.*, 2001; Vollenweider, 2001; Vollenweider and Geyer, 2001) and causes deficits in sustained and spatial attention (Gouzoulis-Mayfrank *et al.*, 2002; Umbrecht *et al.*, 2003; Hasler *et al.*, 2004). In addition, it is well established, based on early phenomenological and psychological studies, that psilocybin and related serotonergic hallucinogens produce a strongly altered experience of time (reviewed in Heimann, 1994), notably a feeling

of slowing down of the passage of time and a subjective overestimation of time intervals expressed in reports that 'minutes appear to be hours' or even that 'time is standing still' (Kenna and Sedman, 1964; Fischer *et al.*, 1966).

To date, alterations in time perception and performance in humans have been linked primarily to the dopamine system (O'Boyle *et al.*, 1996; Rammssayer, 1999), specifically to the cortico-basal ganglia-thalamic-cortical loop representing the neuronal clock (Meck, 1996). Pharmacological studies on animals and humans also support the general hypothesis that fronto-striatal circuits are critical for temporal processing. Dopaminergic antagonists (like haloperidol) that affect the meso-striatal dopamine system disrupt temporal processing in healthy subjects (Rammssayer, 1999). Moreover, animal studies indicate that both dopaminergic agonists and antagonists influence timing processes, presumably by increasing and decreasing clock speed, respectively (Meck, 1996). Patients with Parkinson's disease, who have decreased dopaminergic function in the basal ganglia, and particularly depleting input to the putamen, not only show deficits in motor timing but also in the discrimination of temporal intervals (O'Boyle *et al.*, 1996; Hellström *et al.*, 1997). Thus, intact dopamine neurotransmission within striatal and fronto-cortical sites is important for temporal processing, which is consistent with the notion that a cortico (SMA)-striato-thalamo-cortical system is involved in sensorimotor timing (Harrington *et al.*, 2004). The basic idea in these models is that a pacemaker generates pulses and that the number of pulses represents the subjective estimate of an elapsed interval. The higher the clock rate (presumed to be dependent on the effective dopamine level) the better the temporal resolution will be and the longer subjective estimates of duration (Church, 1984; Matell and Meck, 2004; Harrington *et al.*, 2004; but see Ivry, 1996, who proposes the dominant role of cerebellar mechanisms). Recently, the association of dopaminergic gene loci with endophenotypes of cognitive functioning such as attention and the speed in motor timing was shown (Reuter *et al.*, 2005). Pharmacological manipulations of the serotonin system, applying 5-HT agonists and antagonists, however, have also been shown to affect duration discrimination abilities in humans. Duration discrimination of small intervals with a base duration of 50 ms even improved slightly (Rammssayer, 1989). Given the impairments of patients with schizophrenia in timing tasks, the alterations in subjective time perception in psilocybin model psychosis, and the rather unknown role of the serotonin system in modulating basic timing mechanisms, we designed the present study to elucidate the contribution of the serotonin system to time perception and temporal behaviour. Indications exist that intervals below a time unit of approximately 2 to 3 seconds are processed differently from longer intervals (e.g. Woodrow, 1951; Fraisse, 1984; Pöppel, 1997; Wittmann, 1999). Typically, intervals up to 2 to 3 sec are reproduced accurately, whereas longer intervals tend to be underestimated (Kagerer *et al.*, 2002). Subjects can accurately synchronize their motor actions to a sequence of tones presented with a frequency of approximately 1 to 2 Hz. The ability to synchronize these tones becomes more difficult with increasing inter-tone intervals and finally breaks down when intervals exceed durations of about 2 sec (Mates *et al.*, 1994). Therefore, in the present study

we aimed to investigate dose-dependent effects of psilocybin on temporal control of motor performance in sensorimotor tasks on time ranges below and above 2 to 3 seconds. We hypothesized that psilocybin would affect performance on the longer time ranges given the known elicited deficits in attention and working memory and the importance of working memory in longer duration temporal behaviour. Given the lack of any previous data on the phenomena in question, we did not know what to expect regarding possible decrements of timing performance at shorter time ranges which would indicate fundamental influence on the more basic proposed central pacemaker/accumulator mechanism.

For this double-blind, placebo-controlled experimental study of healthy volunteers, sensorimotor tasks were selected that are standard experimental tools in timing research and have proven to be sensitive measures of behavioural differences between brain-injured patient groups and controls. We employed the tasks of sensorimotor synchronization (Mates *et al.*, 1994), temporal reproduction of time intervals (Kagerer *et al.*, 2002), and personal and maximum tapping speed (Wittmann *et al.*, 2001). Concerning the latter tapping tasks, neuropsychological studies point to a specialization of distinct brain networks associated with either voluntarily-chosen speed or with movements at maximum pace (Wittmann *et al.*, 1999, 2001). This is the first systematic study of timing tasks performed in pharmacological models of psychoses in healthy human subjects. Former studies on time perception in LSD- or psilocybin-induced states in humans reporting the subjective experience of the passage of time (Kenna and Sedman, 1964), each used a single temporal-processing task to assess time-related psychomotor performance. In the study conducted by Fischer *et al.* (1966) self-paced tapping rate during an 8-minute recording period increased in the two subjects exposed to 115 µg/kg psilocybin as compared to the performance of the same subjects on the next day without the drug. Significantly shortened pause durations between the articulations of words were recorded in 12 volunteers who were under the influence of 123 to 174 µg/kg psilocybin. This result was interpreted as evidence for an increase in the speed of a physiological clock (Tosi *et al.*, 1968). However, in a duration identification task with a time range between 300 and 1000 ms, LSD did not affect performance of four subjects (Mitrani *et al.*, 1977). Distinct from these limited measures of timing used previously, our study aims to systematically assess timing performance by investigating the impact of psilocybin on standardized measures of temporal processing. Following from this approach, basic neuropharmacological mechanisms of time perception in the normal brain as well as in psychotic disorders may be elucidated.

Methods and Materials

Subjects

Subjects were students from the University of Zürich and a technical college. Volunteers were supplied with oral and written information about the aim of the study and the effects and possible risks of psilocybin administration. All provided written informed

consent. Eligible subjects had to have normal or corrected-to-normal vision, no hearing problems, were healthy according to medical history, physical examination, clinical-chemical blood analysis and electrocardiogram. Participants were right handed and instructed to use their dominant hand in all experimental tasks. They were also deemed by psychiatric interview to have no personal or family (first-degree relatives) history of a major psychiatric disorder or evidence of regular alcohol or substance abuse. Subjects were also diagnosed according to the DIA-X computerized diagnostic expert system (Wittchen and Pfister, 1997). Administration of psilocybin to healthy subjects was authorized by the Swiss Federal Office of Public Health, Bern. The study protocol was approved by the Ethics Committee of the University Hospital Zürich. Twelve young volunteers (six men and six women; mean age 26.8 years, SD 3.6) were recruited. Six of these participants reported having had previous experience with psilocybin through the ingestion of psilocybe mushrooms (no more than three times) and seven had used cannabis sporadically. All subjects were reimbursed for their time and were informed that they were free to withdraw from the study at any time without reprisal.

Time measures

Temporal reproduction Subjects were instructed to reproduce the duration of a sound at 500 Hz that was presented at comfortable loudness via earphones. Six different standard intervals of 1500 ms, 2000 ms, 2500 ms (short intervals), and 4000 ms, 4500 ms, 5000 ms (long intervals) were used. Each interval was presented randomly eight times, resulting in 48 trials per subject. A trial started with the presentation of a randomly-selected standard interval. After the tone had ended, a fixed-pause interval of 2000 ms duration followed. Then the tone was presented again. Subjects were instructed to reproduce this duration by pressing a key to switch off the stimulus when they believed that the duration corresponded to the previously presented standard interval. After completion of the reproduction phase, a new standard interval was presented. Thus, presentation phases always alternated with reproduction phases. Mean reproduced intervals and the standard deviation of reproduction were calculated over the eight trials per standard interval.

Sensorimotor synchronization Through headphones subjects heard a regular sequence of tonal stimuli that had to be synchronized precisely by tapping the index finger on a key. The intervals between tone onsets were constant. Four different durations of inter-onset intervals were presented in different trials: 700 ms, 1000 ms, 2000 ms and 4000 ms. The number of tones in each trial was varied to achieve a constant trial duration of 56 sec: 80 (700 ms), 56 (1000 ms), 28 (2000 ms), and 14 (4000 ms). Tones had a frequency of 500 Hz and duration of 100 ms. A software program (Mates, 1990) controlled the stimulus presentation and the registration of the inter-tap intervals, as well as recording the asynchrony between the tone onset and the tap onset. As a measure of accuracy of synchronization, the mean asynchrony between tap and tone onset per trial was registered. As a measure of impaired synchronization ability the number of reactions to the

tones per trial was calculated. A reaction to a tone or 'missed synchronization' was defined as a tap onset following a tone with an interval of at least 120 ms. If recorded human reaction times to acoustic stimuli occur less than approximately 120 ms after a stimulus has been presented, they are considered as 'false start', e.g., they were initiated before the stimulus actually occurred (Najenson *et al.*, 1989). Therefore, we defined positive asynchronies (taps occurring after the tone) of more than 120 ms as reactions to the stimulus, that is, as failed attempts to anticipate and synchronize with the repeatedly occurring tone.

Tapping speed Subjects were instructed to tap constantly on a key with the index finger in a personally chosen constant tempo that was neither too fast nor too slow (personal tapping tempo). Then, in a second task, subjects had to tap at maximum speed (maximum tapping tempo). The program by Mates (1990) registered every single inter-tap interval and terminated the program after 20 taps in each task. The median inter-tap interval per trial is calculated as the measure of tapping speed and a coefficient of variance (Interquartile/Median × 100) per trial is taken as a measure of stability of the tapping performance for each person and tapping task.

Cognitive test

Spatial Span test Spatial working memory was assessed using the spatial span (SSP) test taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins *et al.*, 1994). The spatial span test is a computerized version of Corsi's block tapping task measuring the spatial working memory span. For this test, up to nine white boxes arranged irregularly on a black background were presented on a touch screen. During each trial a set number of the boxes were sequentially highlighted by a change in their colour, before returning back to white. Each box was highlighted for the duration of 3 sec. The period between each subsequent box highlighting was 0.5 sec. For each trial the subject was instructed to remember the order in which the boxes were highlighted and then reproduce these changes at the end of the trial by touching the respective boxes in the appropriate sequence. Subjects were initially presented with a sequence of two boxes. After this trial one additional box was added to the sequence after every correct response, up to a maximum of nine boxes. When the subject made a mistake the following trial would repeat the previous number of boxes in a different sequence. After three incorrect responses on any number of boxes, the test was terminated. The final number of boxes that the subject was able to accurately reproduce (Span Length) was recorded.

Psychometric measures

The Altered State of Consciousness rating scale (5D-ASC) (Dittrich, 1998) and the Adjective Mood Rating Scale (AMRS) (Janke and Debus, 1978) were used to assess the subjective effects under placebo and psilocybin. Both the AMRS and 5D-ASC have previously been shown to be sensitive to the psychological effects of psilocybin in humans (Vollenweider *et al.*, 1997, 1998, 1999; Hasler *et al.*, 2004).

5D-ASC The Altered States of Consciousness rating scale 5D-ASC (Dittrich, 1998; Dittrich *et al.*, 1999) consists of 94 items that are visual-analogue scales of 10 cm length. These items measure alterations in mood, perception, experience of self in relation to environment, and thought disorder. Scores of each item range between zero ('No, not more than usually') and ten ('Yes, much more than usually'). The ASC items are grouped into five main factors comprising several items. (1) 'oceanic boundlessness' (OB) measures derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria and/or exaltation as well as alterations in the sense of time. The corresponding item clusters are 'positive derealization', 'positive depersonalization', 'altered time sense', 'positive mood', and 'mania-like experience'. (2) 'anxious ego dissolution' (AED) measures ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. The item clusters are 'anxious derealization', 'thought disorder', 'delusion', 'fear of loss of thought control', and 'fear of loss of body control'. (3) 'visionary restructuring' (VR) includes the item clusters 'elementary hallucinations', 'visual (pseudo-) hallucinations', 'synesthesia', 'changed meaning of percepts', 'facilitated recollection', and 'facilitated imagination'. (4) 'auditory alterations' (AA) refers to acoustic hallucinations and distortions in auditory experiences and (5) the dimension 'reduction of vigilance' (RV) relates to states of drowsiness, reduced alertness, and related impairment of cognitive function.

AMRS The Adjective Mood Rating Scale (AMRS) (Janke and Debus, 1978) consists of 60 adjectives representing different mood states. Subjects were instructed to rate the extent to which each adjective was applicable to their current mood from the options: 'not at all' (1), 'a little' (2), 'quite' (3) and 'strongly' (4). The AMRS consists of the following main factors: 'concentration', 'inactivation', 'tiredness', 'dazed state', 'introversion', 'heightened mood', 'emotional excitability', 'anxiety', 'depressiveness,' and 'dreaminess.'

Experimental procedure

Substance and dosing Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) was obtained through the Swiss Federal Office of Public Health, Bern. Psilocybin capsules (1 mg and 5 mg) were prepared at the Pharmacy of the Cantonal Hospital of Aarau, Switzerland. Quality control comprised tests for identity, purity and uniformity of content. Psilocybin and lactose placebo were administered in gelatine capsules of identical appearance. After oral uptake, psilocybin is rapidly transformed to the pharmacologically active metabolite psilocin (Hasler *et al.*, 1997; Lindenblatt *et al.*, 1998). Usually, first subjective effects of psilocybin are perceived 20 to 40 min after oral administration and peak at about 60 to 90 min to last for another 60 to 120 min. All psilocybin-induced symptoms usually wear off 6 to 8 hours after drug administration (Vollenweider *et al.*, 1997; Hasler *et al.*, 2004).

Study design

We conducted a double-blind, placebo-controlled, within-subject design with three experimental arms: placebo, medium and high doses of psilocybin were administered with a counterbalanced order of administration. Subjects were tested on 3 days separated by at least 14 days to avoid carry-over effects. The medium dose (MD) psilocybin ($115\text{ }\mu\text{g/kg}$; mean body weight of subjects $70.3 \pm 12.5\text{ kg}$; absolute doses $8.2 \pm 1.4\text{ mg}$ psilocybin) and the high dose (HD) psilocybin ($250\text{ }\mu\text{g/kg}$; absolute doses $17.6 \pm 3.2\text{ mg}$ psilocybin) were selected for this study due to observations from a previous investigation (Hasler *et al.*, 2004). These selected doses produced perceptual alterations without producing profound thought disturbances or complete loss of ego control. One week ahead of the first experiment, subjects underwent a somatic and psychiatric examination and were familiarized with the sensorimotor tasks. Subjects arrived at the research unit of the University Hospital of Psychiatry at 8.30 AM on each experimental day, and psilocybin or placebo capsules were administered at 10.00 AM.

Performance on the sensorimotor tasks was assessed just prior to administration of drug/placebo (t_0 ; baseline measures), at 90 minutes during the anticipated peak effects (t_1), and 240 minutes after drug intake (t_2), when effects had decreased substantially. Subjects also underwent psychometric measurements using the AMRS (at 0, 80 and 280 min after drug/placebo administration) and the 5D-ASC (at 110 min). The SSP of the CANTAB battery was accomplished at 0, 100 and 360 min after drug/placebo intake. Subjects were examined by the principal investigator approximately 7 to 8 hours after drug intake and released from the hospital only when the psychotropic effects had completely subsided. The presented results are part of a study that also comprised tests of binocular rivalry (sampled at 100 min, 180, 270 and 360 min), these results are reported separately (Carter *et al.*, 2005).

Statistical analysis

Psychometric data were analysed using a one-, two- or three-way repeated measures ANOVA. Analysed factors were (1) treatment (placebo, MD psilocybin, HD psilocybin), (2) time of measurement (t_0, t_1, t_2) and – where applicable – (3) measures or subscales (different temporal intervals in a timing task or subscales on a questionnaire). The interaction of treatment \times time of measurement was considered as the main source of information since the effect of psilocybin should occur at t_1 and to a lesser degree at t_2 , in contrast to the placebo condition. In cases where a significant interaction effect was observed, simple a priori contrasts compared differences between placebo and both MD and HD psilocybin. These drug dose effects were considered in respect to changes over time from both t_0 to t_1 and t_0 to t_2 (four contrasts). In some cases we looked at the three treatment conditions separately. Then, time of measurement (t_0, t_1, t_2) was the main factor in three drug conditions followed by two contrasts each (t_0 to t_1 and t_0 to t_2). Pearson's correlation analysis was used to compare relative change in performance on the temporal-processing tasks, the spatial span working memory test and the 5D-ASC rating scale. Only those correlations found to be significant at both medium and

high doses were considered. For these cases, the low and high dose data were pooled to calculate a single Pearson's r value for that measure.

To minimize the possible effects of non-normal distribution in the data sets, we transformed all data prior to analysis by applying a natural log transform. In the case that negative values had to be transformed, a constant was added to the variable to make sure that all values were positive. Additionally, Greenhouse-Geisser adjustment of degrees of freedom was applied to the data set when, according to the Mauchly test, sphericity of the sample distributions could not be assumed. Significance levels were set to values of $p < 0.05$. However, since multiple comparisons were planned for each measure, the risk of Type I error increases (incorrect rejection of null hypothesis). To ensure overall protection level, only those planned contrasts associated with the decisive interaction for hypothesis testing (e.g. time of measurement \times treatment) on each measure are reported. Nevertheless, we adjusted the alpha level for each measure to the amount of contrasts that were applied (e.g. two contrasts: $p < 0.025$, four contrasts: $p < 0.0125$) as well as for the number of ANOVAs that were calculated for different subscales of a task.

Results

Temporal reproduction

To test for an effect of psilocybin on temporal reproduction, three-way repeated measure ANOVAs were calculated separately for the short (1500 ms, 2000 ms, 2500 ms) and the long intervals (4000 ms, 4500 ms, 5000 ms). The three main factors included were interval duration (three intervals for the short and the long intervals, respectively), measurement time (t_0, t_1, t_2) and treatment (placebo, MD and HD psilocybin). For the short intervals, interval duration was the only factor to show a significant effect [$F(2,16)=600.2, p < 0.001$], reflecting a linear increase in reproduction intervals as a function of the presented interval duration (see Figs 1a–1c). No other main factors or interactions showed significant differences. For the long intervals, significant main effects of interval duration [$F(2,16)=130.0, p < 0.001$] and measurement time [$F(2,16)=6.9, p=0.007$] were revealed. The interaction treatment \times measurement time, the decisive interaction to reveal differential drug effects between peak and baseline, proved to be significant [$F(4,32)=3.2, p=0.025$]. No other interaction revealed a significant effect.

To discern the treatment \times measurement-time interaction at the long intervals, we looked separately at the three treatment conditions that were tested at the three measurement times. For every treatment condition, a two-way ANOVA with the interval duration (4000 ms, 4500 ms, 5000 ms) and measurement time (t_0, t_1, t_2) was calculated. In the placebo condition (Fig. 1a), we found a significant difference for the factor interval [$F(1,8)=98.1, p < 0.0001$], but no significant effect of measurement time and no significant interaction of measurement time \times interval duration. A similar result was obtained for MD psilocybin (Fig. 1b): a significant difference was only revealed for the factor interval [$F(2,20)=122.7,$

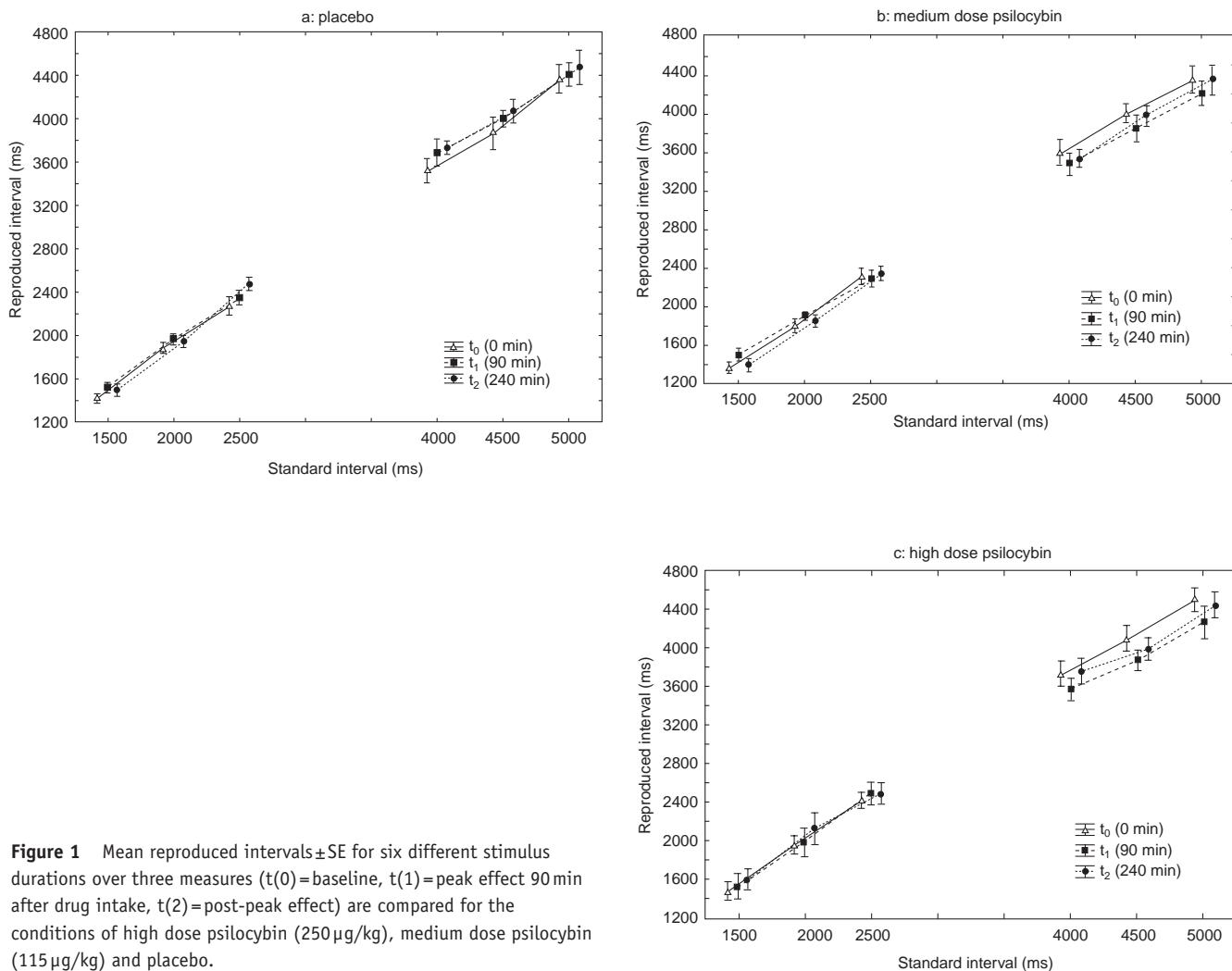


Figure 1 Mean reproduced intervals \pm SE for six different stimulus durations over three measures (t_0) = baseline, (t_1) = peak effect 90 min after drug intake, (t_2) = post-peak effect) are compared for the conditions of high dose psilocybin (250 µg/kg), medium dose psilocybin (115 µg/kg) and placebo.

$p < 0.0001$] and measurement time did not reach the significance level ($p < 0.1$). The interaction between interval duration and measurement time also revealed no significant effect. In the treatment condition HD psilocybin (Fig. 1c), however, the ANOVA revealed significant effects for both main factors, interval duration [$F(2,22) = 49.5, p < 0.001$] and measurement time [$F(2,22) = 7.0, p = 0.004$]; no significant interaction effect was found. As depicted in Fig. 1c, temporal reproductions at the long intervals showed a stronger tendency toward underestimation at peak time of HD psilocybin as compared with baseline. Contrasts for the effect of measurement time in the HD-psilocybin condition showed significant differences for the contrast between t_1 and t_0 [$F(1,11) = 13.0, p = 0.004$] but no significant difference between t_2 and t_0 [$F(1,11) = 0.36, p = 0.561$]. Thus, HD psilocybin leads to a significant under-reproduction of time intervals of 4 seconds and longer.

To assess the stability of performance, we compared the standard deviation of the reproduced interval for the three factors:

interval, measurement time and treatment. A three-way ANOVA for the short intervals did not reveal any significant effects. For the long intervals, measurement time showed a significant effect. However, for both, the long and short interval durations, the treatment \times measurement time interaction failed to reach the significance level.

Sensorimotor synchronization

Asynchrony (Mean) To assess the subjects' ability to temporally synchronize to a regularly occurring external stimulus, a three-way ANOVA with the main factors: treatment, measurement time and interval (700 ms, 1000 ms, 2000 ms, 4000 ms) was calculated for the dependent variable asynchrony. Whereas the effect of treatment failed to reach significance [$F(2,22) = 3.0, p = 0.069$], measurement time [$F(2,22) = 10.1, p = 0.001$] and interval [$F(1.2,13.5) = 16.7, p < 0.001$; Greenhouse-Geisser adjusted] showed significant differences. Moreover, the measurement time

\times treatment interaction was found to be significant [$F(4,44)=3.9, p=0.009$]. The interaction between interval and measurement time failed to reach significance [Greenhouse-Geisser adjusted]. The interaction of interest (measurement time \times treatment) only tended towards significance for the contrast between HD psilocybin and placebo between t_1 and t_0 [$F(1,11)=4.5, p=0.057$] but a significant difference was observed for the contrast between MD psilocybin and placebo between t_1 and t_0 [$F(1,11)=14.5, p=0.003$].

To take a closer look at the treatment \times measurement-time interaction, we calculated two-way ANOVAs separately for the three treatment conditions with the two main factors: measurement time and interval. In the placebo condition, only the main factor interval [$F(1.2,13.2)=13.6, p=0.01$; Greenhouse-Geisser adjusted] proved to be significant. No significant differences were found for either measurement time or the interval \times measurement-time interaction (Fig. 2a). In the MD-psilocybin condition both

factors interval [$F(1.27,33)=12.4, p=0.002$; Greenhouse-Geisser adjusted] and measurement time [$F(2,22)=10.2, p<0.001$] revealed significant differences, but not the interaction of the two. Contrasts for the effect of measurement time in the MD-psilocybin condition showed a significant difference for the contrast between t_1 and t_0 [$F(1,11)=16.9, p=0.002$] but no significant difference between t_2 and t_0 [$F(1,11)=0.669, p=0.431$] (Fig. 2b). In the HD psilocybin condition, interval [$F(1.4,15.9)=9.9, p=0.003$; Greenhouse-Geisser adjusted] and measurement time [$F(2,22)=8.1, p=0.002$] as well as the interval \times measurement-time interaction [$F(2.5,27.7)=4.7, p=0.012$; Greenhouse-Geisser adjusted] reached the significance level. Contrasts for the effect of measurement time in the HD-psilocybin condition revealed only a marginally significant difference (adjusted p value) for the contrast between t_1 and t_0 [$F(1,11)=5.5, p=0.039$] and no significant difference between t_2 and t_0 [$F(1,11)=1.844, p=0.202$] (Fig. 2c). It is to note that the smaller mean asynchrony between tap and tone

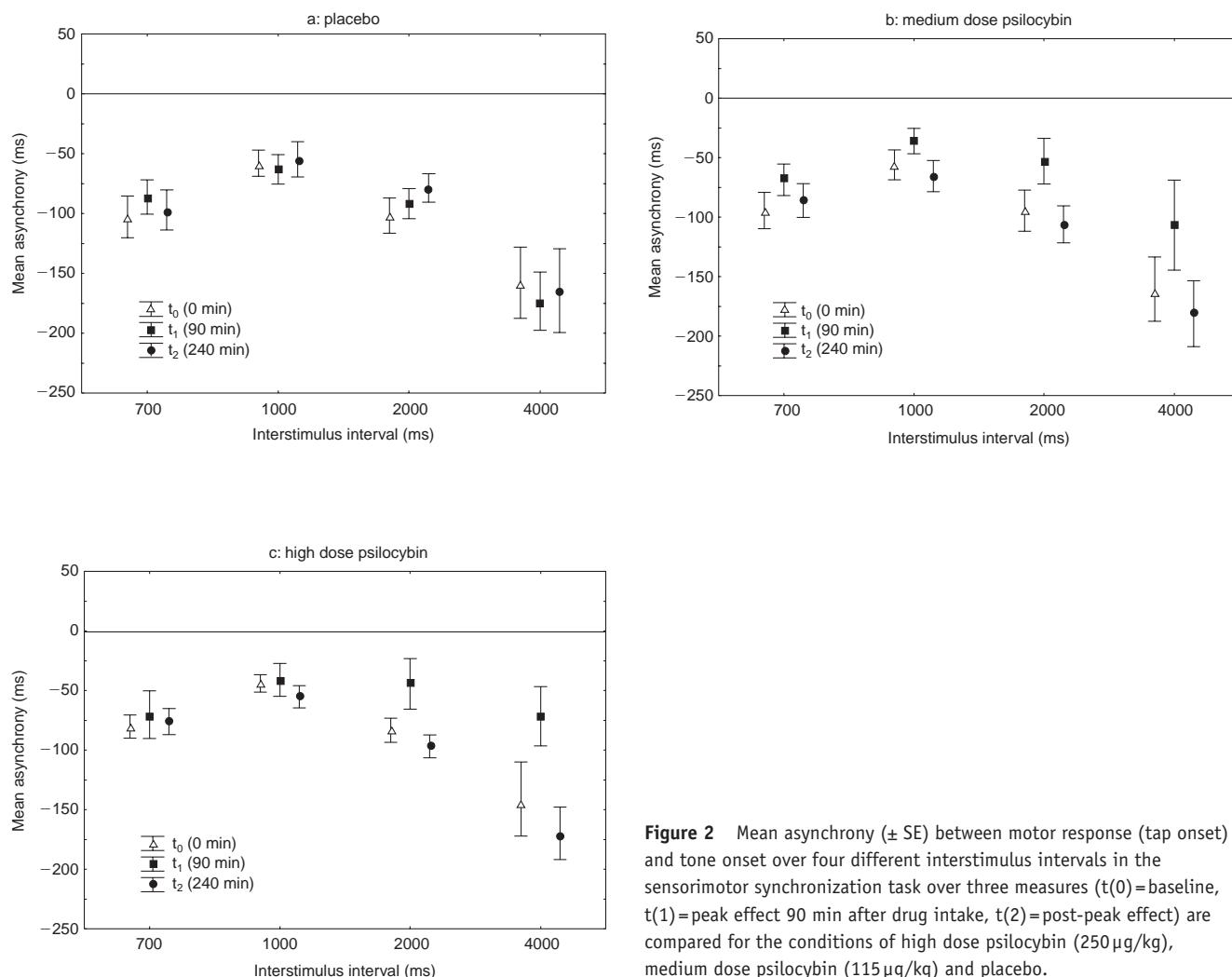


Figure 2 Mean asynchrony (\pm SE) between motor response (tap onset) and tone onset over four different interstimulus intervals in the sensorimotor synchronization task over three measures (t_0 =baseline, t_1 =peak effect 90 min after drug intake, t_2 =post-peak effect) are compared for the conditions of high dose psilocybin (250 μ g/kg), medium dose psilocybin (115 μ g/kg) and placebo.

onset does not reflect a more precise synchronization ability but instead an increase in reaction times, that is, more missed synchronizations (see below).

Asynchrony (standard deviation) To measure the stability of synchronization performance, the standard deviation of the asynchrony between the tap and the tone was taken as the dependent variable in a three-way ANOVA with the main factors: treatment, measurement time and interval. Treatment [$F(2,22)=1.4, p=0.874$] and time of measurement [$F(2,22)=1.6, p=0.229$] showed no effect on performance. The length of the inter-beat interval had a significant influence on tapping variability [$F(3,33)=227.5, p<0.001$] – the standard deviation getting bigger with increasing intervals. However, the important interaction measurement time \times treatment [$F(4,44)=1.4, p=0.268$] was not significant.

Per cent missed synchronization As can be seen in Fig. 3a–c, it was only for the 2- and 4-seconds intervals that a considerable

amount of reaction time asynchronies (> 120 ms) were detectable. Therefore, only these two intervals were taken for further calculations. A three-way ANOVA comparing the per cent missed synchronization for the factors – treatment, measurement time and interval (2000 ms, 4000 ms) – showed a significant main effect only for treatment [$F(2,22)=4.9, p=0.018$] and interval [$F(1,11)=16.5, p=0.002$]. The interaction in focus of our hypotheses treatment \times measurement time showed not to be significant [$F(4,44)=1.1, p=0.37$] although – descriptively – subjects show more reaction times under psilocybin at peak-time than at baseline or at post peak (see Fig. 3a–c).

Personal tapping speed

A two-way ANOVA (treatment and measurement time) revealed that psilocybin significantly slowed tapping tempo. There was a main effect of measurement time [$F(2,20)=3.5, p=0.05$], treatment [$F(2,20)=4.9, p=0.019$], and the measurement time \times treat-

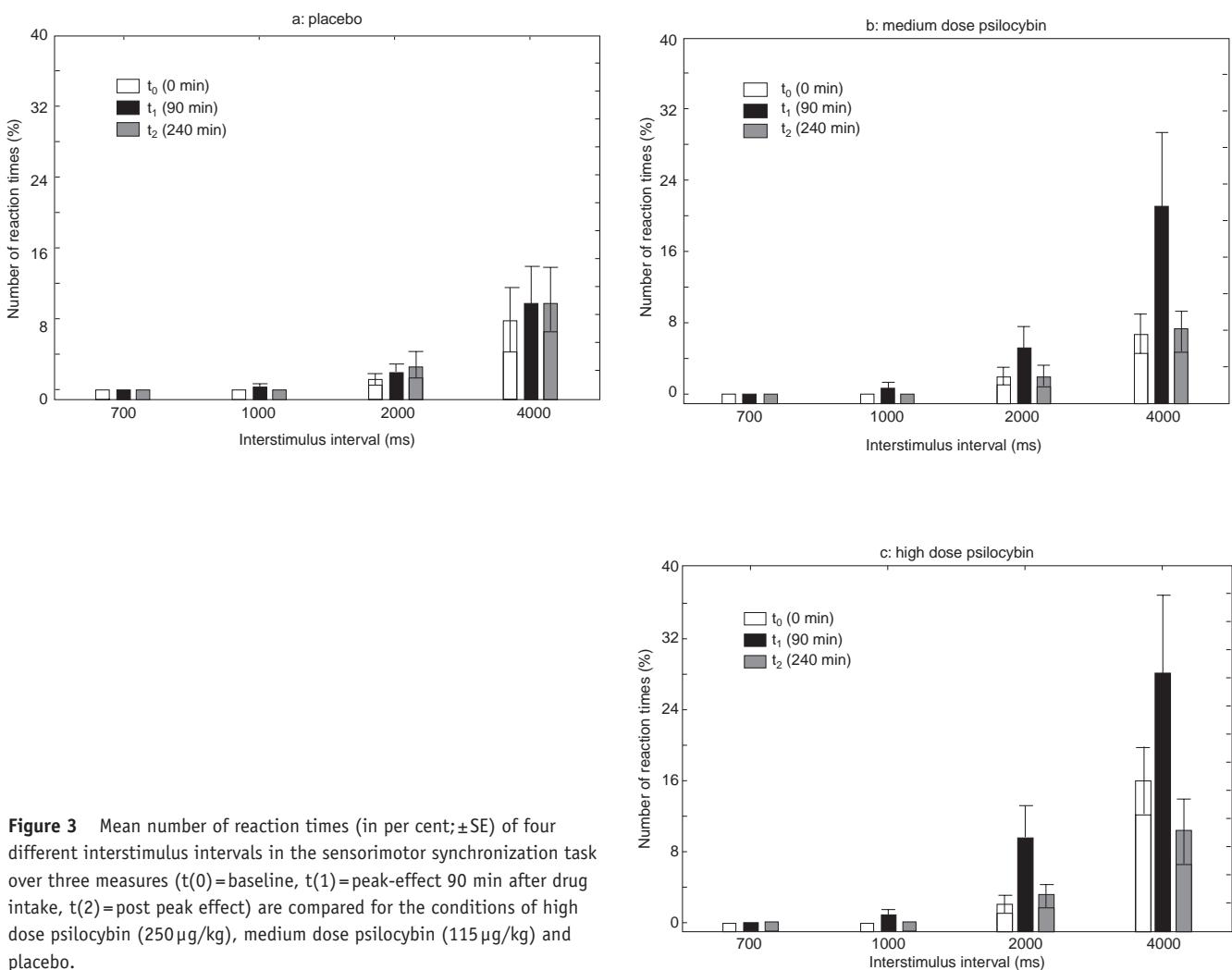


Figure 3 Mean number of reaction times (in per cent; \pm SE) of four different interstimulus intervals in the sensorimotor synchronization task over three measures (t_0 = baseline, t_1 = peak-effect 90 min after drug intake, t_2 = post peak effect) are compared for the conditions of high dose psilocybin (250 µg/kg), medium dose psilocybin (115 µg/kg) and placebo.

ment interaction [$F(4,40)=3.1, p=0.026$]. Subjects tapped slower during peak effects of HD psilocybin (949.0 ms, SD: 390.0) than at baseline (692.2 ms, SD: 274.6) and post-peak effects of drug (772.1 ms, SD: 280.7). Following a one-way ANOVA with the factor measurement time in the HD condition [$F(2,20)=8.7, p=0.002$], subsequent contrasts reveal a significant difference between t_1 and t_0 [$F(1,10)=13.6, p=0.004$] but no significant difference between t_2 and t_0 [$F(1,10)=2.7, p=0.133$]. No effect of measurement time was seen in the MD condition [$F(2,20)=1.5, p=0.247$]. The coefficient of variance, the measure for tapping stability in the personal tempo, revealed a significant main effect of measurement time [$F(2,20)=5.7, p=0.01$], but no effect for treatment or the interaction of the two main factors.

Maximum tapping speed

Over the different experimental conditions, subjects' maximum tapping speed was registered with mean inter-tap intervals of approximately 150 ms. Two-way ANOVA for the factors measurement time [$F(2,22)=10.9, p=0.001$] and treatment [$F(2,22)=4.3, p=0.026$] showed significant main effects. However, the important measurement time \times treatment interaction was not significant. Since the main effect of treatment includes the t_0 and t_2 measurement times in addition to the t_1 measurement time, the treatment effect was probably due to by chance different performance on the psilocybin administration day. Furthermore, a two-way ANOVA on the coefficients of variance for the inter-tap interval showed no significant main effects or interaction, suggesting that tapping stability at maximum speed is unaffected by psilocybin.

Spatial span task

Two-way ANOVAs (factors treatment and measurement time) were calculated to elucidate the effects of psilocybin on the spatial

span length. We found no overall effect for treatment [$F(2,22)=1.33, \text{n.s.}$], a significant effect to measurement time [$F(2,22)=4.05, p=0.032$], and – decisive for the question of concern – a significant interaction effect [$F(2,22)=4.66, p=0.003$]. A priori contrasts (alpha level adjusted to $p<0.0125$ for four contrasts) revealed a significant difference only for the contrast between placebo and HD psilocybin between t_1 and t_0 ($p<0.011$). Thus, at the peak of effects, HD psilocybin (and not MD psilocybin) impaired spatial span task (SSP) performance as indexed by span length (see Fig. 5).

Altered States of Consciousness rating scale (5D-ASC)

As shown in Fig. 4, psilocybin increased the scores of the 5D-ASC dimensions (as assessed at peak time) in a dose-dependent manner. There was a main effect of treatment [$F(2,22)=14.2, p<0.001$]. The main effect for subscale did not reach the significance level [$F(2.22,24.2)=4.38, p=0.064$; Greenhouse-Geisser adjusted] but the treatment \times subscale interaction did [$F(8,88)=2.53, p=0.016$]. Subsequent one-way repeated measures ANOVAs comparing the three treatment conditions at peak time were performed for each of the five subscales (adjusted alpha level for five comparisons is $p<0.01$). A significant effect of treatment could be seen in all five subscales: OB [$F(2,22)=13.54, p<0.001$; contrast for MD psilocybin vs placebo: $p=0.01$; contrast for HD psilocybin vs placebo: $p<0.001$], AED [$F(2,22)=7.08, p=0.004$; MD psilocybin vs placebo: $p=0.046$ (n.s.); HD psilocybin vs placebo: $p=0.005$], VR [$F(2,22)=11.2, p<0.001$; MD psilocybin vs placebo: $p=0.006$; HD psilocybin vs placebo: $p=0.003$], AA [$F(1.368,15.05)=9.79, p=0.004$; Greenhouse-Geisser adjusted; MD psilocybin vs placebo: $p<0.167$ (n.s.); HD psilocybin vs placebo: $p=0.007$], RV [$F(2, 22)=7.67, p=0.003$; MD psilocybin vs placebo: $p=0.004$; HD psilocybin vs placebo: $p=0.003$].

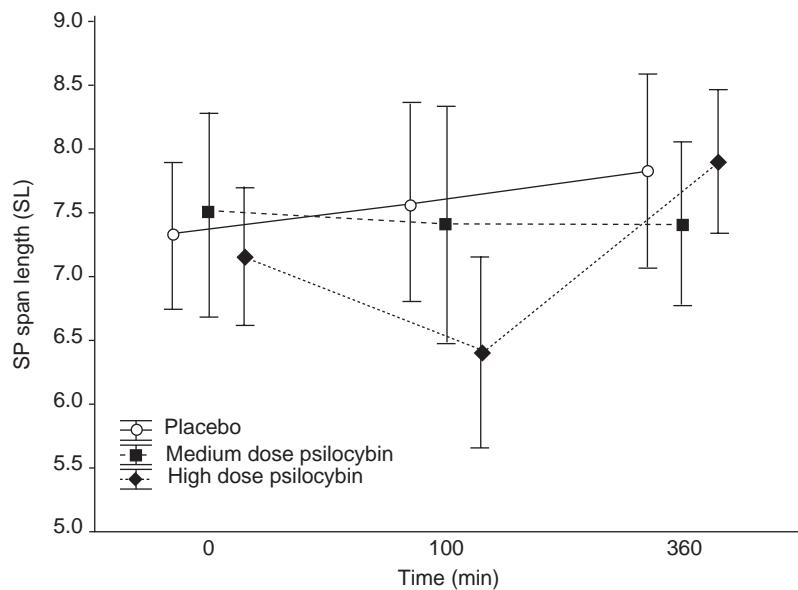


Figure 4 Dose- and time-dependent effects of psilocybin on working memory performance as indexed by spatial span length (SL; mean \pm SE).

A subsequent exploration of the ASC item clusters in each subscale revealed that the increase in OB after high-dose psilocybin was mainly due to moderate increases in (positive) 'derealization phenomena' ($30.8 \pm 18.7\%$ of scale maximum), 'heightened mood' ($30.1 \pm 18.9\%$) and 'mania-like symptoms' ($26.0 \pm 18.5\%$). The item of special interest, 'altered time sense', also showed a significant effect of psilocybin [$F(1,33,14.61)=7.9, p=0.009$; contrast for MD psilocybin vs placebo: $p=0.083$ (n.s.); contrast for HD psilocybin vs placebo: $p=0.017$]. The increase in AED was attributable to moderate 'thought disturbances' ($45.0 \pm 29.8\%$ of scale maximum) followed by slight increases in 'loss of body control' ($20.1 \pm 21.0\%$), 'loss of thought control' ($15.9 \pm 28.5\%$) and 'anxious derealization' ($15.0 \pm 23.4\%$). Furthermore, the analysis of the VR item-cluster revealed that only the high dose, but not the medium dose of psilocybin significantly produced 'complex hallucinations' and increased 'facilitated recollection and imagination,' and that increase in VR after medium dose of psilocybin was mainly due to visual illusions and elementary hallucinations, such as light flashes or geometric figures.

Adjective Mood Rating Scale (AMRS)

Two-way repeated measures ANOVAs were performed for each of the ten subscales (adjusted alpha level: $p<0.005$). A significant interaction between treatment and measurement time, was found for the subscales of inactivation [$F(4,44)=7.89, p=0.001$; significant contrast for MD psilocybin vs placebo between t_0 and t_1 ($p<0.001$) as well as between HD psilocybin and placebo between t_0 and t_1 ($p=0.019$)], tiredness [$F(4,44)=6.6, p<0.001$; MD psilocybin vs placebo between t_0 and t_1 ($p<0.001$)], dazed state [$F(4,44)=6.51, p<0.001$; MD psilocybin vs placebo between t_0 and t_2 ($p<0.001$)], introversion [$F(4,44)=9.84, p<0.001$; MD psilocybin vs placebo between t_0 and t_2 ($p<0.001$)], emotional excitability [$F(4,44)=5.36, p<0.001$; MD psilocybin vs placebo

between t_0 and t_1 ($p=0.015$)], and dreaminess [$F(4,44)=12.4, p<0.001$; MD psilocybin vs placebo between t_0 and t_1 ($p=0.009$) as well as t_0 and t_2 ($p<0.001$)]. A tendency for a treatment \times measurement-time interaction was found for the subscale of 'concentration' [$F(4,44)=4.12, p=0.006$]. No significant interaction effect appeared for the subscales of heightened mood, anxiety and depressiveness. The effects of psilocybin on the AMRS mood scales during peak time, comparing the three treatment conditions, are presented in Fig. 6.

Correlations between working-memory performance, time measures and psychometric scores

Correlational analyses revealed no significant correlation between spatial span length and temporal reproduction for the longer intervals (4000, 4500, 5000 ms; where significant drug effects were found) (r ranged from -0.17 to 0.16). However, there was a strong negative correlation between spatial span length and the OB subscore ($r=-0.73, p<0.001$). Further multiple regression analysis revealed that the two OB items 'depersonalization' and 'altered time sense' contributed most to this effect ($r=-0.83, p<0.0001$ and $r=-0.69, p<0.001$, respectively). Importantly, the other factors on the 5D-ASC did not show significant correlations with spatial span length, indicating that this effect was specific and not a generalized association between the drug-induced altered state of consciousness and working-memory decrement. There were no significant correlations between any of the temporal-processing measures and the 5D-ASC subscales, however a trend towards correlation between the OB subscore and the time reproduction underestimation at longer time intervals was found. Specifically, the item 'altered time sense' showed moderate correlation coefficients with the longer time intervals in temporal reproduction at peak time under the influence of MD and HD psilocybin: the larger the underestimation of the 4500 and 5000 ms

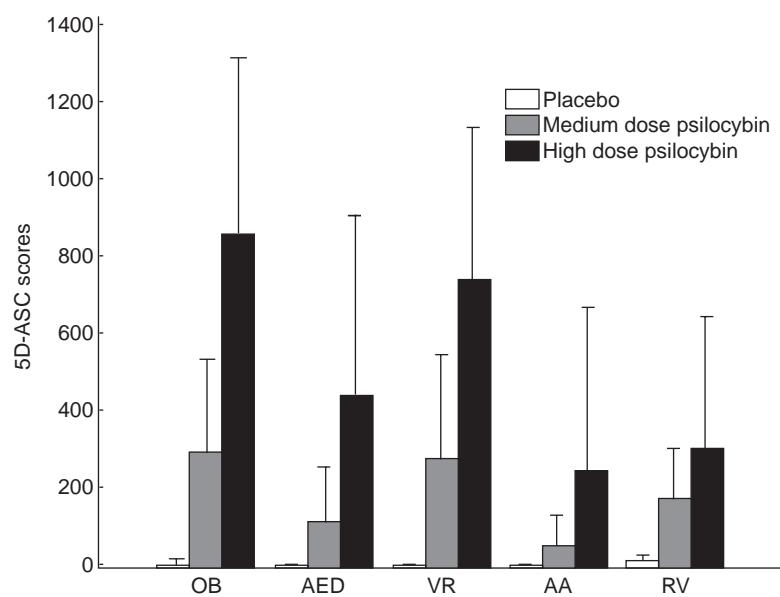


Figure 5 Mean scores \pm SE of the Altered States of Consciousness Rating Scale (5D-ASC) during the peak effect of high dose psilocybin (250 µg/kg) compared to medium dose psilocybin (115 µg/kg) and placebo ($n=12$). OB=oceanic boundlessness, AED=anxious ego dissolution, VR=visionary restructuring, AA=auditory alterations, RV=reduction of vigilance.

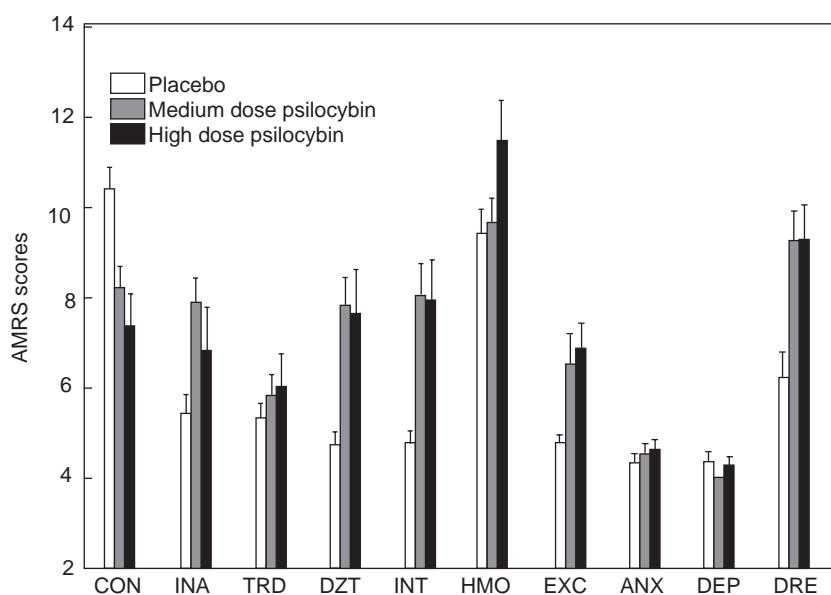


Figure 6 Mean scores \pm SE of the Adjective Mood Rating Scale (AMRS) during the peak effect of high dose psilocybin (250 µg/kg) compared to medium dose psilocybin (115 µg/kg) and placebo ($n=12$). CON = concentration, INA = inactivation, TRD = tiredness, DZT = dazed state, INT = introversion, HMO = heightened mood, EXC = emotional excitability, ANX = anxiety, DEP = depressiveness, DRE = dreaminess.

interval, the higher the score on the 'altered time sense' item (r between 0.4 and 0.6). However, these associations failed to reach the significance level.

Discussion

Our investigation clearly revealed that the 5-HT_{2A}/5-HT_{1A} mixed agonist psilocybin alters time perception and temporal control of behaviour in humans. These results confirm self-reports that hallucinogens cause strong alterations in spatial and temporal perception (Vollenweider *et al.*, 1997; Hasler *et al.*, 2004) and extend these psychometric findings by showing the specific ways in which objective measures of temporal processing can be affected. Psilocybin was found to affect an individual's capacity to accurately reproduce interval lengths longer than 3 seconds, synchronize a motor response (finger tap) to regular auditory beats with intervals longer than 2 seconds, and to slow down the personal tapping tempo (preferred tapping rate). No impairment of performance was observed for shorter lengths on the sensorimotor synchronization and the reproduction task. This indicates that the effects found at the longer intervals were likely a product of interactions with cognitive dimensions of temporal processing instead of interactions with the proposed basic pacemaker/accumulator mechanisms of the brain (Rammsayer, 1999; Wearden, 2004).

Several studies on timing point to a temporal-integration interval of approximately 2 to 3 sec that can be found in perception and motor performance (for reviews, see Fraisse, 1984; Pöppel, 1997; Wittmann, 1999). Durations of temporal intervals in the temporal-reproduction task are estimated precisely with intervals up to approximately 2 to 3 sec, whereas longer intervals are substantially underestimated (Kagerer *et al.*, 2002). A temporal limitation of anticipatory planning is also observed in the sensorimotor syn-

chronization task. The ability to synchronize accurately becomes substantially weaker when the inter-stimulus interval is longer than 2 sec (Mates *et al.*, 1994). Our pharmacological approach contributes to these findings, as psilocybin mildly affects only those intervals of longer duration in each task. One of the few time perception studies under LSD in humans adds to our results (Mitrani *et al.*, 1977): subjects did not show distortions in the ability to identify durations of visual stimuli in the range between 300 ms and 1 sec although they reported changes in the subjective passage of time.

In respect to the current model of timing with multiple processing stages (Wearden, 2004), the disturbed timing abilities for sensorimotor synchronization and duration reproduction we show here could reflect impairments of short-term memory, attention or decision-making mechanisms (Zakay and Block, 1996; Pouthas and Perbal, 2004), rather than the alteration of the pacemaker-accumulator clock (the basic internal timing mechanism). This is especially supported by the concurrent deficits observed in working memory in the present study. Converging evidence exists for the involvement of working memory in temporal reproduction. Processing of a secondary task that influences working-memory capacity interferes with the encoding and reproducing of durations in the domain of seconds (Fortin and Rousseau, 1998). Miyake *et al.* (2004) showed that a secondary working-memory task affected the accuracy of synchronization only with inter-stimulus intervals above 2 seconds. With inter-stimulus intervals below 2 seconds the memory task had no influence on performance. In a group of elderly subjects, working memory capacity correlated with performance in a temporal reproduction task with durations of 5 and 14 seconds (Baudouin *et al.*, 2006). Frontal regions known to be closely linked with working-memory function, particularly dorsolateral and frontomedial cortices (Postle *et al.*, 2000; Cabeza and Nyberg, 2000; Owen, 2000) are active during temporal reproductions of time intervals of

a few seconds (Elbert *et al.*, 1991; Volz *et al.*, 2001; Monfort and Pouthas, 2003). Given the selective effect of psilocybin on the longer duration intervals in both the temporal reproduction and sensory synchronization tasks it seems that the temporal disturbance observed is induced through interference with cognitive processes like attention and working memory. The fact that no correlations were found between performance on the working-memory and temporal-processing tasks, should not be considered as evidence against this hypothesized role of working memory in the observed timing impairments. Rather it is likely to reflect the small sample size combined with the relatively small effect sizes seen in both the timing measurements and the working memory. In fact, the small impairments observed for the timing measures may reflect a relative insensitivity of working memory performance to psilocybin, a claim supported by the finding that psilocybin had no significant effect on working memory at either the median dose used in this study (115 µg/kg) or a higher dose (215 µg/kg) used in a separate study (Carter *et al.*, in press). However, further studies are warranted to corroborate this interpretation. Moreover, it is also possible that other working-memory functions such as verbal working memory might be more significantly associated with the timing tasks.

Whereas the maximum-tapping speed was unaffected by psilocybin, the tapping tempo in a voluntarily chosen tempo was significantly slower during peak effects of HD psilocybin as compared to baseline and post-peak time of that condition. This finding is consistent with several lines of evidence showing that the control of motor speed can basically be characterized by two distinct sensorimotor processes functioning with different frequencies. For example, movements with a frequency of 1 to 2 Hz are under voluntary control and allow the collection of somatosensory information (feedback control), while movements at maximum speed with frequencies of 5 Hz and above require only coarse pre-attentive control (feed-forward control) (Peters, 1989; Kunesch *et al.*, 1989; Wittmann *et al.*, 1999). These two sensorimotor modes appear to be controlled by distinct neural networks. Injury of the cerebellum can lead to dysdiadochokinesia, the inability to alternate agonist and antagonist muscles with maximum speed (Dichgans, 1984). In contrast, metabolic dysfunction of the basal ganglia such as in Parkinson's disease can lead to the inability to tap at a slower pace, patients showing the so-called hastening phenomenon (Nakamura *et al.*, 1978). In another study, tapping in a self-paced tempo was slowed down in patients with left-hemispheric lesions to the brain, whereas maximum-tapping speed was not influenced by lesions in either side of the cortex (Wittmann *et al.*, 2001). The effect of HD psilocybin on personal tapping tempo, leading to a slower pace of the regular finger taps at peak time, could be the result of the drug influencing cortical sites of the brain, including those of the left hemisphere. In partial support of such a hypothesis we have previously found that psilocybin caused left-over-right sided dorsolateral overactivation that significantly correlated with depersonalization phenomena using FDG-PET imaging (Vollenweider *et al.*, 1997; Vollenweider, 2001).

Psilocybin-induced dose-dependent changes to subjective measures of conscious state, i.e. the loosening of ego boundaries, changes in affect and perceptual distortions as previously reported

in detail (Vollenweider *et al.*, 1997; Hasler *et al.*, 2004), included the expected changes in time perception as indexed by the 5D-ASC item 'altered time sense'. Although we found no correlation between working-memory deficits and the objective timing measures used, we did find significant correlations between working-memory impairment and subjective measures of altered time sense and depersonalization experiences measured by the OB subscale of the 5D-ASC. The trend towards correlations for the duration underestimation above 3 seconds and the OB item 'altered time sense' merits further studies seeking to investigate the relationship between alterations in temporal processing and experiences of self.

The pharmacological basis of the experience of time and temporal processing is only vaguely understood. Pharmacological manipulations in animal and human studies indicate that dopaminergic agonists and antagonists influence timing processes – supposedly by increasing and decreasing (respectively) clock speed (Rammsayer, 1989; Cevik, 2003). The detrimental effect of the DA antagonist haloperidol on duration discrimination with base intervals of 50 ms has been interpreted as resulting from a slowing down of the clock rate (Rammsayer, 1989). Studies in patients with Parkinson's disease show that dopaminergic agonists can improve motor timing (O'Boyle *et al.*, 1996). It appears that dopaminergic neurotransmission within striatal and cortical sites is strongly connected to temporal processing, leading to the postulation of a cortico-striato-thalamo-cortical system involved in sensorimotor timing (Matell and Meck, 2004). The present results indicate that the serotonin system is also involved in temporal processing, either directly as a component of one of the basic processing stages in the model of timing or indirectly by influencing dopaminergic or glutaminergic transmission as we have previously shown in PET studies of psilocybin model psychosis (Vollenweider *et al.*, 1999). When taking into account the different levels of the timing model that are an integrative part of the cognitive system (Pouthas and Perbal, 2004), several neurotransmitter systems play a decisive role in temporal processing in the range of seconds. Rammsayer (1999), for example, discovered that the dopamine receptor antagonist haloperidol as well as benzodiazepine midazolam had detrimental effects on duration discrimination of intervals ranging around 1 second whereas processing of 50-ms intervals was only affected by haloperidol. These results were discussed as influences via disruption of transmitter-guided cognitive processes such as attention and working memory. The author concluded that any pharmacological treatment that affected working-memory capacity would interfere with temporal processing of intervals in the longer time range. It has to be noted that we did not find effects of psilocybin on durations below 2 seconds. This discrepancy can only be resolved in future studies that consider task-specific and pharmacological factors. In addition to comparing possible task-related differences between the duration discrimination task and the sensorimotor tasks used in our study, selective effects of individual pharmacological substances will probably be accounted for by the inconsistencies found over different studies. In the study presented here, the 5-HT_{2A/1A} receptor agonist psilocybin affected time intervals in sensorimotor synchronization and temporal reproduction only above 2 to 3 seconds and

only self-paced tapping (and not maximum tapping). These effects can also be interpreted as following the disruption of cognitively mediated temporal-processing stages. Moreover, as we are reporting the specific effects of the drug concerning the time domain, we can rule out the possibility that a generally decreased capacity of subjects to interact with the environment or a decreased interest for the experimental task produced the effects shown.

Our main goal was to elucidate whether psilocybin induced specific effects on temporal control of behaviour and, if so, whether these would be a function of the duration of the processed time interval – an effect we did find. In future studies the possible relationship between duration processing and underlying cognitive functions including different aspects of working memory – for example, taking into account differences between spatial and verbal working memory – needs to be further investigated by concurrently probing other dimensions of attention and working memory. Further studies with specific 5-HT_{1A}, 5-HT_{2A} and dopamine receptor antagonists are needed to tease out the relative contribution of each of these receptor systems to the observed effects. In respect to the use of psilocybin in modelling endogenous psychosis, temporal processing deficits have been observed in chronic medicated schizophrenics at both short and long intervals (Davalos *et al.*, 2002, Davalos *et al.*, 2003, Elvevag *et al.*, 2003) whereas our current findings indicate that only longer interval processing is affected by psilocybin. It would be of interest to see whether the use of the same paradigm in healthy subjects with psilocybin and unmedicated acute schizophrenic subjects would show the same disparity of effects. Moreover, as some effects could be seen on a descriptive level but differences failed to reach the significance level it would be interesting to investigate whether increasing the number of participating subjects may yield further effects of the psilocybin intervention.

Acknowledgments

This study was supported by the Heffter Research Institute, Santa Fe, NM, USA, and the Swiss Federal Office of Public Health (BAG contract No. 00.001023) through grants to FXV. The authors especially thank G. Greer, MD, for critical comments on the manuscript.

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